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ARTICLE

The role of ultrasound in the detection of cervical lymph node metastases in clinically N0 squamous cell carcinoma of the head and neck

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Abstract

Nodal involvement is the most important prognostic factor in head and neck squamous cell carcinoma (HNSCC) of mucosal origin. The presence of a single ipsilateral or contralateral metastatic node reduces survival by 50% and bilateral disease by a further 50%. The management of N+ HNSCC is relatively clear-cut. By contrast, the investigation and treatment of patients with clinically N0 disease is controversial. Most institutions electively treat the neck with surgery or radiotherapy because the risk of occult metastases is over 20%, even though it will be unnecessary in the majority of cases. In this situation the main purpose of staging would be to assess those nodes that are not going to be removed. However, the optimal management of the clinically N0 neck remains controversial and there is growing interest in a more conservative approach. Research is now directed toward finding a method of staging sensitive enough to bring the risk of occult metastases below 20%. High spatial resolution, ease of multiplanar scanning, power Doppler and the ability to perform guided fine-needle aspiration for cytology give ultrasound (US) an advantage over other imaging techniques.

Keywords: *Imaging; lymph node; cervical; staging; ultrasound; carcinoma; metastases; head and neck neoplasms; fine needle aspiration; biopsy; cytology.*

Introduction

The average survival rates from head and neck squamous cell carcinoma (HNSCC) of mucosal origin is about 50% and has improved only modestly in the last few decades[1]. Nodal involvement is the most important prognostic factor[2]: there are around 400–700 nodes in the head and neck but the presence of a single ipsilateral or contralateral metastatic node reduces survival by 50% and bilateral disease by a further 50%[3].

Our understanding of the detection of cervical lymph node metastases in HNSCC is complicated by conflicting literature and rapid advances in imaging, histological and surgical techniques. Exciting developments are on the horizon but for now the technique of choice depends on local skills and resources and on the local approach to surgical and oncological management.

Most centres stage cervical lymph nodes at the same time as the primary cancer using either computer tomography (CT) or magnetic resonance imaging (MRI). This is straightforward when there are clear signs of metastatic involvement such as significant enlargement, matting, necrosis or extra-capsular spread. The difficulty comes in assessing small nodes without malignant features. The spatial resolution of high frequency ultrasound (US) is now so good that small structures such as the vagus nerve, which are not routinely visible on CT or MRI, can be clearly demonstrated (Fig. 1a and b). High spatial resolution combined with ease of multiplanar scanning, power Doppler and the ability to perform

guided fine-needle aspiration for cytology (USFNAC), gives US an advantage over CT and MRI in staging cervical lymph nodes.

The management of patients with HNSCC and palpable nodal disease is relatively clear-cut. By contrast, the investigation and management of patients with clinically N0 disease is controversial. Most institutions electively treat the neck with surgery or radiotherapy because the probability of occult metastases is greater than 20%, even though it will be unnecessary in the majority of cases. However, there is growing interest in a more conservative approach and the method, extent and even the need for elective treatment is a matter of debate[4]. Clearly, the efficacy of lymph node staging in N0 HNSCC is of increasing importance.

In order to avoid the unnecessary treatment of histologically negative necks, a staging technique must be sensitive enough to reduce the risk of occult metastases to <20%, i.e. have a negative predictive value (NPV) of >0.8. Bayesian logic states that 'the probability of a disease being present given that a test is negative depends on the pre-test probability or the prevalence of the disease and the sensitivity and specificity of the test' as described by the following formula[5]:

$$\frac{1}{1-NPV} = \frac{1}{P(D+/T+)} = \frac{\mathrm{Pr}(1-\mathrm{Sn})}{\mathrm{Sp}(1-\mathrm{Pr}) + \mathrm{Pr}(1-\mathrm{Sn})}$$

where NPV is the negative predictive value, P is unknown, Pr is the pre-test prevalence (%), $D+$ are true negatives, T+ are true positives, Sn is the sensitivity (%) and Sp is the specificity (%).

For example, for an investigation with a specificity of 100%, if occult metastases occur in 30% of patients with N0 HNSCC, a sensitivity of at least 42% is required to avoid treatment (Table 1).

The reported incidence of occult metastases in clinically N0 HNSCC ranges from 29.3% to 44%, mostly clustered around 40%[6–10]. In order to avoid elective treatment in these patients, using the formula above, the minimum sensitivity required of a staging technique with a specificity of 80% is 70% and with a specificity of 100% is 63%. But sensitivity and specificity are characteristics of the study population being tested, not of the test itself. This means that one cannot extrapolate results from a study on HNSCC patients with mixed nodal staging to a group of patients with N0 disease[11]. Unfortunately, very few studies have been specifically designed to determine the sensitivity of staging criteria in the N0 sub-population.

Matters are further complicated by the growing realisation that manifestations of metastatic disease that are only evident microscopically such as extra-nodal soft tissue deposits (STDs), microscopic ECS and micrometastases, are common in patients with HNSCC and may be associated with a poor prognosis. Defined as intranodal deposits of tumour <3 mm in size, micrometastases have been found in 25% of positive neck dissections from patients with clinically N0 HNSCC and were the only manifestation of metastatic disease in 8% of these patients[12–14]. The biological and prognostic significance of micrometastases in HNSCC is uncertain, although some studies report an association with

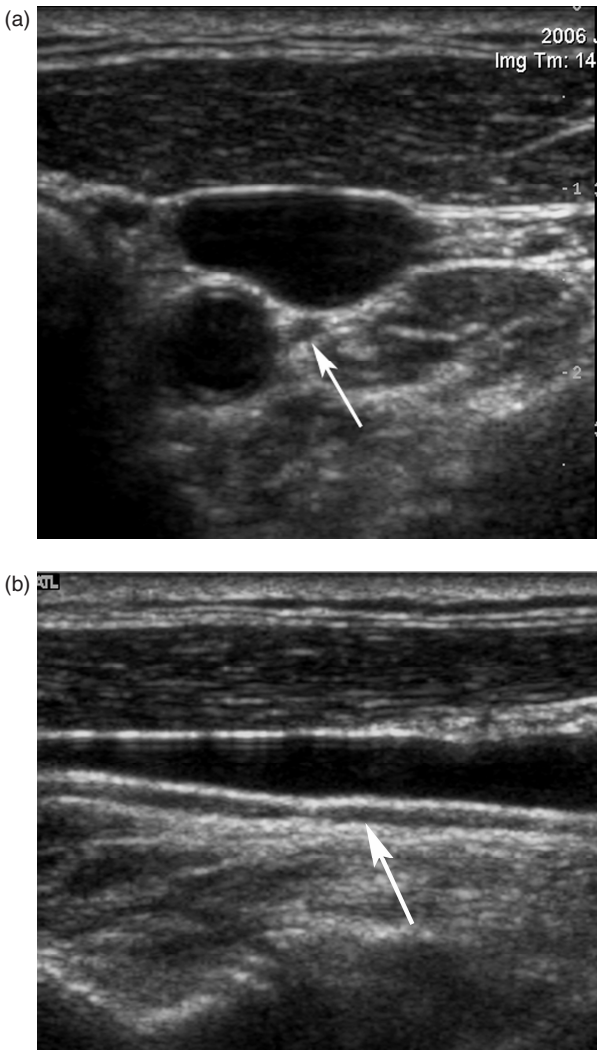

Figure 1 **Ultrasound of the carotid sheath demonstrating the vagus nerve (arrow) in both the transverse (a) and longitudinal (b) plane.**

Table 1 Sensitivity of staging necessary to avoid elective surgery

Pre-test prevalence of occult metastases (%)	Sensitivity (%) required to reduce risk of occult metastases to 20% for test with specificity of 80%	Sensitivity (%) required to reduce risk of occult metastases to 20% for test with specificity of 100%
50	80	75
45	76	70
40	70	63
35	63	54
30	53	42

reduced survival[15]. Microscopic ECS has recently been reported to have a similar detrimental effect on prognosis to macroscopic ECS, reducing the 3-year survival of patients with nodal metastasis from 72% to 36%[2]. STDs are thought to occur by total replacement of a lymph node or some other process such as lymphatic tumour embolisation. They have been reported in around 8% of clinically N0 patients and there is evidence that they may also be associated with reduced survival[16,17].

The detection of micrometastases and microscopic ECS is beyond the scope of any form of imaging and there is little relevant literature on the imaging of STDs. Even their histological demonstration is dependent on the commitment of the pathologist[17,18]; the number of lymph nodes examined, the number and thickness of sections taken and the use of immunhistochemistry and molecular analysis[14,15,18–22]. If one accepts the premise that these microscopic entities may have an impact on prognosis, elective treatment becomes mandatory once again and the major role of staging reverts to assessing those nodes that will not be removed at surgery.

So what is the role of US and USFNAC? US has many advantages over CT and MRI. It has the greatest soft tissue spatial resolution and can demonstrate sub-millimetre structural detail beyond the scope of CT or MRI; compare the appearances of the vagus nerve on US with MRI (Fig. 1a and b). Multiplanar imaging and the assessment of vascular pattern with power Doppler are easy and if in doubt, fine needle aspiration can be performed. There are pitfalls however (Table 2). Cross-sectional imaging is still required to assess retropharyngeal and paratracheal nodes that are inaccessible to US. The technique is operator dependent with a steep learning curve for both the sonologist and cytopathologist[23–26]. By the end of 18 months staging HNSCC with US and USFNAC, Knappe *et al.* found that the average examination time had fallen from 45 to 10 min with a parallel fall in non-diagnostic samples from 22% to <10%[26]. There is an inverse relationship between nodal size and the ability to obtain sufficient material with the majority of non-diagnostic samples being taken from nodes <5 mm in size[7,24,25]. Finally, there can be some difficulty in correlating a suspicious node with cross-sectional imaging and follow up US and in indicating the exact location to the surgeon.

Table 2 Pitfalls of US and USFNAC

Misses retropharyngeal, retrotracheal and nasopharyngeal nodes
Multiple aspirations per patient
Operator dependent
Difficulty biopsying nodes <4 mm in size
Difficulty indicating exact location for surgeon
Difficulty correlating with cross-sectional imaging
Difficulty correlating with follow up US

Size is still routinely used to discriminate metastatic nodes from normal by cross-sectional imaging. A size criterion acts as a filter and any nodes smaller than the mesh will be missed. Sensitivity can be increased by reducing the size cut-off, but at the cost of lower specificity and an increase in the false positive rate. There have been numerous attempts to determine the optimal size threshold, although wide variations in the criteria applied and in the nodal dimension measured (i.e. maximum long axis, minimum or maximum short axis) make it difficult to draw firm conclusions from the literature. Furthermore, very few studies have been restricted to the N0 sub-group.

In 1998 Van den Brekel's team published a seminal paper looking at the relationship between clinical staging and the sensitivity of size criteria[11]. They used US to measure the minimum axial diameter of nodes from a consecutive series of 184 surgically treated patients with HNSCC, approximately half of which had clinically N0 disease. The pre-test prevalence of occult metastases in the N-all group was 58% and in the N0 sub-group was 39%. Table 3 shows sensitivity and specificity values for a range of diameters and demonstrates the effect of changing the population characteristics from N-all to N0. For the group of patients taken as a whole, a threshold of ≥10 mm had a sensitivity of 63% and specificity of 92%. By comparison the same threshold performed far worse in the N0 sub-group with a sensitivity of only 16% although the high specificity was maintained.

Based on these figures, the size criteria giving the optimal compromise between sensitivity and specificity in the N0 sub-group was ≥6 mm (≥7 mm for level II). This threshold achieved a post test probability of <0.2 and therefore could be used to follow a watch and wait policy. However, with a specificity of 59% and positive predictive value (PPV) of only 0.55, about 65% of patients would still require treatment, around half of which unnecessarily.

Although predicating nodal metastases by neck side is probably of greater clinical relevance, it is interesting to note that when van den Brekel went on to break down

Table 3 Sensitivity and specificity of size criteria irrespective of nodal staging vs. N0 HNSCC (thresholds for level II were 1 mm larger)

Minimum axial diameter (mm) as measured on US	Sensitivity/ specificity in N-all (%) (248 neck sides)	Sensitivity/specificity in N0 sub-group (%) (131 neck sides)
≥4	95/31	90/33
≥5	94/40	86/44, NPV 0.83, PPV 0.49
≥6	91/52	80/59, NPV 0.82, PPV 0.55
≥7	83/70	61/76, NPV 0.62
≥8	74/78	41/84
≥9	69/88	27/95
≥10	63/92	16/98
≥11	57/97	10/99

Table 4 Sensitivity and specificity of size criteria at different levels in N0 HNSCC (thresholds for level II were 1 mm larger)

Minimum axial diameter (mm) as measured on US	Sensitivity/specificity in N0 sub-group (%) (131 neck sides)		
	Level I	Level II	Level III–IV
≥4	79/68, NPV 0.84	87/41	68/68, NPV 0.77
≥5	71/71	87/50	63/76
≥6	57/80	81/63, NPV 0.84	53/91
≥7	43/91	77/77	43/96
≥8	21/96	58/84	32/97
≥9	14/99	39/91	11/100
≥10	7/100	29/95	11/100

the figures level by level, the calculations indicated that an even smaller threshold of 4 mm was required for levels I, III and IV in order to support a wait and watch policy (Table 4).

The overall accuracy of a highly sensitive staging technique should be increased by combining with a second more specific parameter. Several such parameters have been evaluated.

Shape

Shape is usually described in terms of the ratio between the maximum longitudinal and transverse diameters (L/T ratio). Normal lymph nodes are usually elliptical with an L/T ratio of >2 (Fig. 2) whereas metastatic nodes tend to be rounder (Fig. 3). In 1995 Steinkamp *et al.*[27] published a prospective study using US to assess the size and shape of 730 nodes in 285 patients with N-all HNSCC. Using an L/T ratio of <2 to predict metastases, both benign and malignant nodes were correctly identified with a sensitivity of 95%. The majority of nodes were >10 mm in minimum axial diameter although the trend appeared to extend to smaller nodes. The significance of shape in N0 HNSCC has yet to be directly investigated however. Whilst shape may be a sensitive criterion in the assessment of nodes it is not very specific. Reactive lymphadenopathy, tuberculosis and lymphoma are also characterised by round nodes[28].

Echogenicity

Metastatic lymph nodes are typically hypoechoic to skeletal muscle but this is non-specific. When Ahuja *et al.* looked at 286 enlarged lymph nodes in patients with a range of pathologies including TB, lymphoma and metastases, they found that 81–100% of the metastatic nodes were hypoechoic compared to skeletal muscle as were 100% of lymphomatous and tuberculous and reactive nodes[28].

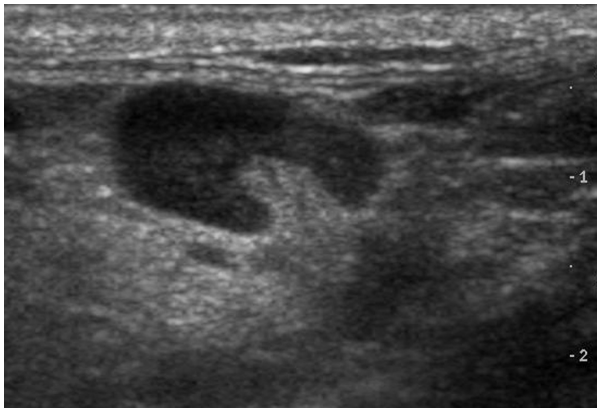

Figure 2 **Normal elliptical node with echogenic hilum.**

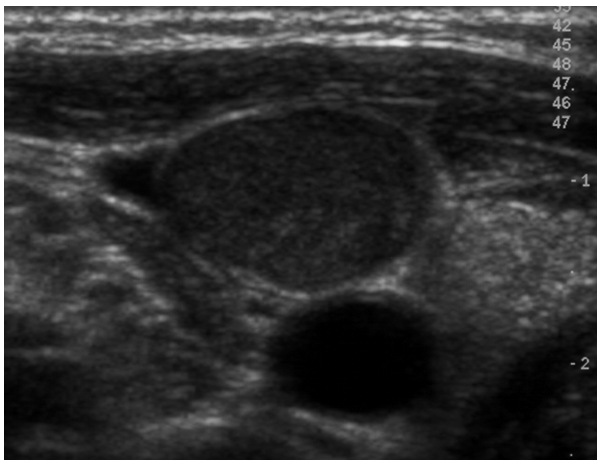

Figure 3 **Round metastatic node with L/T ratio ≤2.**

Echogenic hilum

Most normal lymph nodes have an echogenic hilum caused by the interfaces between lymphatic sinuses as they converge on the medulla (Fig. 2)[29], but neither the presence nor absence of the hilum is a reliable indicator of nodal status[30]. Reported figures vary. In the largest study, Yuasa *et al.* looked at 458 nodes in patients with N-all HNSCC, and found the echogenic hilum was missing in 90% of the metastatic nodes. However, it was also missing in 44% of benign nodes and is therefore non-specific, i.e. when present, the node is highly likely to be benign, but when absent it could be either[31].

Granular parenchymal echoes

By contrast, granular parenchymal echoes, believed to represent coagulation necrosis, keratin or viable tumour, are highly specific for metastases (Fig. 4). In the same study, Yuasa found granular parenchymal echoes in 57% of metastatic nodes and they were

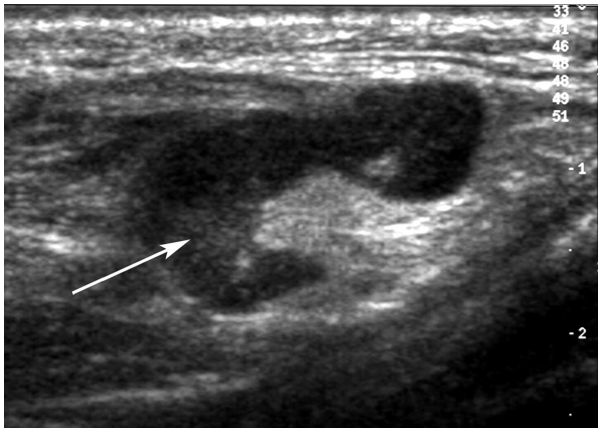

Figure 4 **Granular parenchymal echoes.**

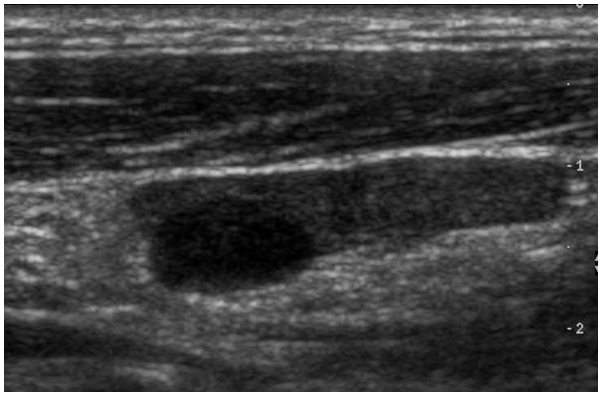

Figure 5 **Focal intranodal metastatic deposit.**

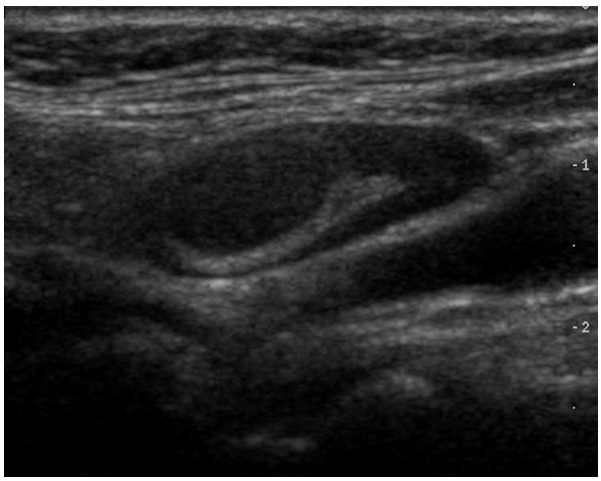

Figure 6 **Focal cortical widening associated with focal hilar distortion.**

absent in 99% of benign nodes, i.e. if you see them the node is very unlikely to be benign[31].

Grouping

The influence of nodal distribution on predicting metastases in HNSCC has been investigated by several authors. In their 1990 histopathological study, van den Brekel *et al.* found that, when combined with minimum axial diameter, the presence of groups of three or more nodes of borderline size at appropriate drainage sites increased sensitivity at a high specificity[32]. Further supportive evidence came from Close *et al.* who assessed 61 patients with N-all HNSCC by CT and reported that the presence of multiple otherwise benign looking nodes in a high risk area correctly predicted metastases in 61%[33]. The significance of such nodal grouping in N0 HNSCC has still to be evaluated.

Focal intranodal deposits and cortical thickening

Intranodal metastatic deposits are occasionally demonstrated on US as areas of focal hypo or hyperechogenicity (Fig. 5). Cortical thickening without changes in echotexture has also been proposed as a sign of intranodal metastatic involvement, especially when associated with focal hilar narrowing (Fig. 6), but this phenomenon can only be assessed if an echogenic hilum is present to provide a reference structure. Vassallo *et al.* described isolated focal cortical thickening in 25% of 17 metastatic nodes from a spectrum of tumour types but in none of a series 24 benign nodes. Concentric cortical thickening was seen in 70% of malignant nodes but also occurred in reactive lymphadenopathy[34]. Further supporting literature is sparse.

Necrosis

Lymph node necrosis is common and highly specific for HNSCC metastases[32,35–45]. Its presence is a poor predictive sign for response to both chemo- and radiotherapy. Necrosis occurs when a tumour mass outgrows its blood supply. In coagulative necrosis the node becomes a homogeneous eosinophilic mass as a result of the coagulation of denatured protein and is hyper- or isoechoic to normal nodes (Fig. 7). In liquefaction necrosis the cells are digested by their own lysosomal enzymes resulting in a more cystic appearance (Fig. 8). Necrotic nodes are often surrounded by an inflammatory stroma and may be matted (Fig. 9).

Necrosis was thought to occur relatively late in the evolution of disease[3,37], characteristically after extensive tumour infiltration and rarely in nodes <1 cm. However, several studies have now demonstrated necrosis in subcentimetre nodes. Eida's group found that 35% of all the necrotic metastatic nodes detected by CT in a group of 59 patients with N0 HNSCC were <10 mm in short axis diameter[6]. Friedman *et al.* looked at 69 neck dissection

specimens from patients with N-all HNSCC and detected necrosis in 33% of metastatic nodes measuring <10 mm in diameter[38]. Thus, a point should be made of searching for necrosis when staging N0 HNSCC.

King and co-workers have published the only study to directly compare the detection of necrosis by US, CT and MRI[39]. In 27 patients with N-All HNSCC, 89 of 903 nodes were positive at histology of which 43 contained areas of necrosis. The sensitivity of both MRI (93%) and CT (91%) was significantly better for necrosis than US (77%) but the specificity of all three techniques was similar, ranging from 89% to 93%. None of the modalities could reliably detect necrotic areas of 3 mm or less or differentiate between necrosis and other focal change due to tumour such as keratin, fibrous tissue and viable tumour.

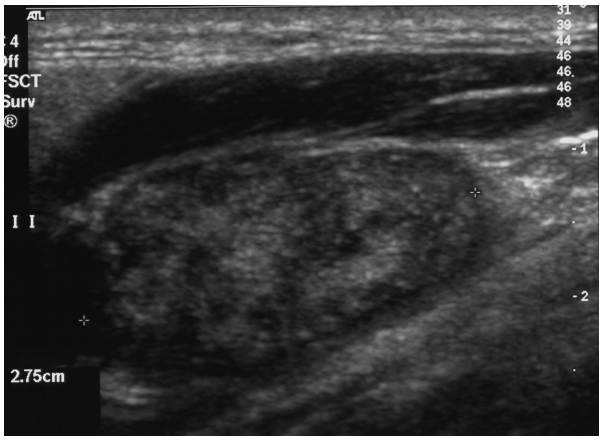

Figure 7 **Coagulation necrosis.**

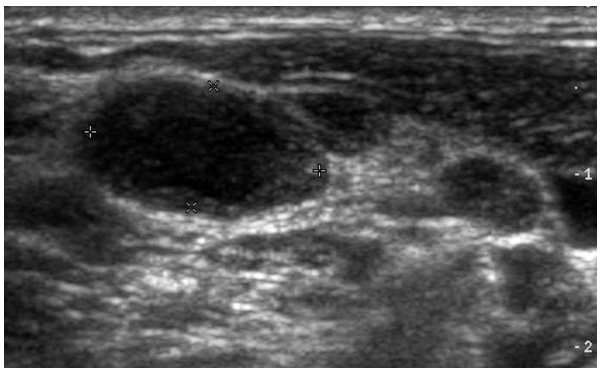

Figure 8 **Liquefaction necrosis.**

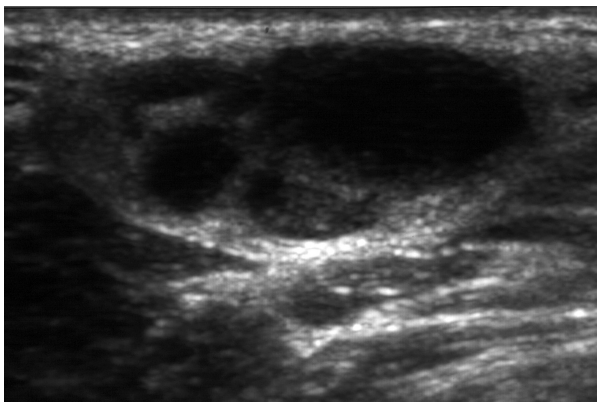

Figure 9 **Multiple metastatic lymph nodes with extranodal stroma causing matting.**

Extracapsular spread

Extracapsular spread (ECS) is common, being reported in 20–46% of metastatic nodes from HNSCC[16,17,37,40]. Its presence increases the risk of local recurrence tenfold[40] and significantly decreases survival compared to patients who have pN0 or pN+ disease without ECS[2,16]. ECS is characterised by irregular nodal margins on US (Fig. 10a and b). Steinkamp *et al.* examined 110 patients with N-all HNSCC for ECS with US and reported a sensitivity of 79% with a specificity of 82% which was comparable to CT and MRI[41]. However, ECS is not confined to late stages of disease.

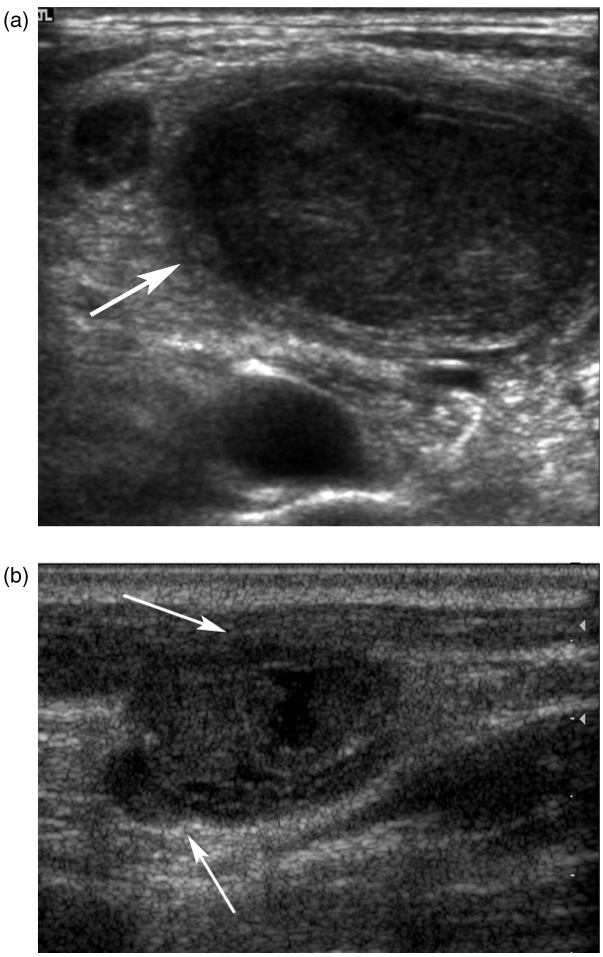

Figure 10 **Extracapsular spread.**

When Don *et al.* examined 957 nodes from 36 patients with N-all HNSCC, they found that although the incidence of ECS increased with nodal size, 30% of nodes with ECS were <10 mm and 12% were <5 mm in longitudinal axis[37]. Woolgar reported histological evidence of ECS in 16% of HNSCC patients staged as N0 by CT[2]. There is no literature on the detection of ECS by US in N0 HNSCC although it is unlikely to be very sensitive in small nodes.

Vascular pattern

Power Doppler is the modality of choice for the assessment of vascular pattern (VP) because it is most suitable for the detection of weak signal and low Doppler shift frequencies, it does not alias, it is not angle dependent and gain can be increased without filling the image with noise. Six main VPs are described: avascularity (Fig. 11); a hilar pattern where vessels radiate out from the hilum into the node (Fig. 12); vascular displacement due to the presence of a focal intranodal lesion (Fig. 13); a parenchymal pattern where vessels are distributed chaotically within the node; a peripheral pattern due to neovascularisation where vessels enter the node via the capsule away from the hilum (Fig. 14); and a mixed pattern in which elements from more than one pattern are combined (Fig. 15). Avascularity is not a good discriminator of metastatic from benign nodes in HNSCC[42,43]. By comparison hilar and non-hilar patterns appear highly specific for benign and metastatic nodes respectively[6,35,42–46].

The overall accuracy of VP improves further when combined with size, shape and other grey-scale features although there is no literature restricted to N0 HNSCC. Yonetsu *et al.* assessed VP and size in 338 nodes from 73 patients with N-All HNSCC[45]. They concluded that a maximum axial diameter threshold of ≥8, ≥9 and ≥7 mm for levels I, II and III–IV respectively, gave the best compromise between sensitivity (≥78%) and specificity (≥90%). However, when combined with VP, the high specificity of hilar flow for benign disease allowed size thresholds to be lowered to improve sensitivity. When the cut-off was adjusted to ≥6, ≥7 and ≥5 mm for levels I, II and III+IV respectively, the sensitivity of VP combined with size was ≥89% with a specificity of ≥94%.

Ariji and co-workers combined VP with shape in a study of 71 metastatic and 220 benign lymph nodes from 77 patients of which 66 had N-All HNSCC[43]. Only nodes ≥5 mm were included in the study. The authors found that peripheral or parenchymal VP predicted metastases with a sensitivity of 83% and specificity 98%. However, when combined with shape using an L/T ratio of ≤1.5, these values were even more impressive with a sensitivity of 92% and specificity of 100%.

Ahuja's group looked at VP and grey scale features in 101 metastatic nodes from a mixed population of

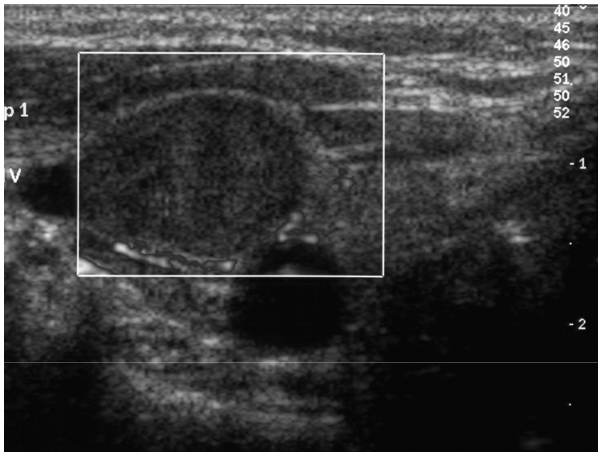

Figure 11 **Avascular vascular pattern.**

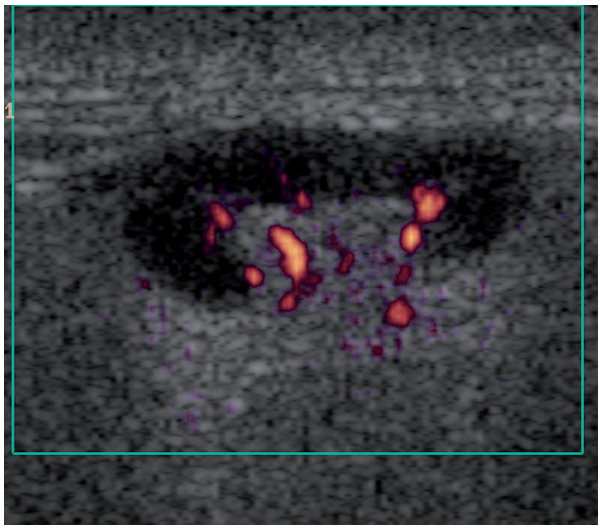

Figure 12 **Hilar vascular pattern: vessels radiate out from the hilum.**

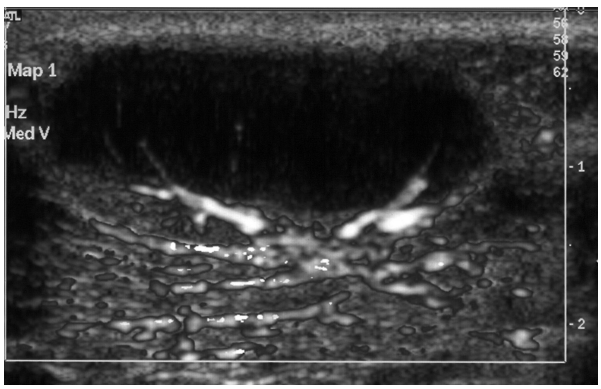

Figure 13 **Vascular displacement due to focal intranodal necrosis.**

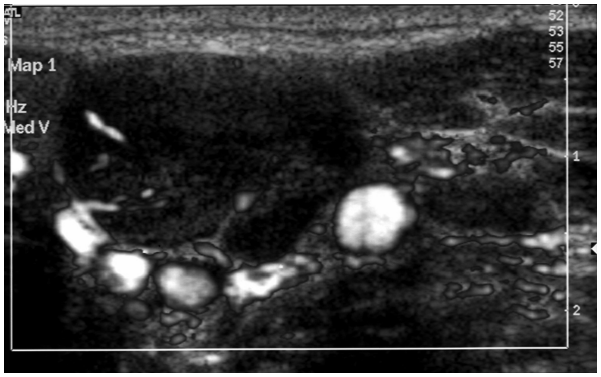

Figure 14 **Peripheral vascular pattern: vessels enter through the capsule away from the hilum.**

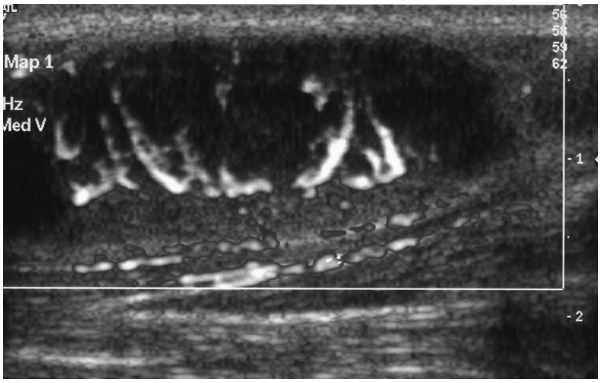

Figure 15 **Mixed pattern: in this example both parenchymal and peripheral VPs are combined.**

tumours and 72 non-metastatic nodes[35]. Neither VP nor grey scale could classify metastatic nodes in 10% and 5% of patients respectively, but VP aided the diagnosis in 5% of patients with metastatic and 17% of patients with non-metastatic nodes. Using a minimum of three features to denote malignancy (abnormal internal echogenicity, deranged internal architecture and an L/T of ≤ 2.0), grey-scale alone had a sensitivity of 95% and specificity 83%. By comparison, VP had a sensitivity of 90% and specificity of 100%. However, when VP and greyscale parameters were combined, both sensitivity and specificity reached 100%.

It has been argued that VP is only unreliable in small nodes because flow volume may be too low to be detectable. The use of micro-bubble contrast agents facilitates the differential diagnosis of nodes ≥ 5 mm in size by identifying additional vessels and demonstrating VP in more detail[47]. Moritz *et al.* examined 94 nodes ≥ 5 mm in size in 39 patients with N-All HNSCC, combining size, shape, texture and margin with VP studies, pre and post contrast[48]. The use of contrast revealed additional vessels in 28% of nodes, increasing the sensitivity of VP combined with grey-scale from 81% to 100%. Specificity increased from 88% to 98% with an overall accuracy of 99%. Although yet to be established, contrast is likely to enhance the diagnostic power of VP in nodes ≤ 5 mm as well.

Intranodal vascular resistance

Resistive and pulsatility indices tend to be slightly higher in metastatic nodes than benign, believed to result from neoangiogenesis and arteriovenous shunt formation[6,46,49,50]. Several papers have suggested that these parameters can be used to detect metastases[36,42–45], but considerable overlap in results between benign and malignant nodes means the technique is not specific and a role in staging HNSCC remains to be established.

Ultrasound-guided fine needle aspiration cytology (USFNAC)

USFNAC is 100% specific for nodal metastases in HNSCC[7,8,23,24,30,51–54]. The reported sensitivity in N0 HNSCC ranges from 42% to 73% but this depends on the criteria used to select nodes for aspiration. It is also affected by more operator dependent factors such as the rate of false negative aspirates and non-diagnostic samples. False negative aspirates occur when the wrong node or wrong part of the node is aspirated or if the cytopathologist fails to spot small quantities of tumour cells. Non-diagnostic samples are too hypocellular or haemodilute to exclude disease. Both are more frequent the smaller the node being aspirated.

Many authors believe that the combination of US and USFNAC is so accurate in N0 HNSCC they can stop electively treating the neck[24,30,51–54]. The largest study came from van den Brekel's team who combined US determined size criteria and USFNAC to stage 77 patients with clinically N0 HNSCC[24]. USFNAC was performed on any node >4 mm in minimum short axis diameter (>5 mm at level II). All patients with negative US or USFNAC were managed conservatively with regular clinical and US review. Nodal recurrence was seen in 18%, corresponding to an overall sensitivity of 82%. Seventy-one percent of these patients were treated successfully. As the overall false negative rate of this staging strategy was <20%, they felt able to justify a watch and wait policy.

Molecular analysis and immunohistochemistry have been reported to detect nodal metastases in 15% of patients deemed pN0 at routine histology. These techniques can also be performed on cytology specimens and may reduce the chances of getting a false negative result. Nieuwenhuis *et al.* examined 235 USFNAC samples from patients with HNSCC. Fifty-nine percent of non-diagnostic aspirates were positive on molecular evaluation for the squamous cell specific antigen E48 mRNA using PCR[55]. The authors suggest that

molecular analysis should be performed on all negative and non-diagnostic USFNAC samples.

Comparison of US and USFNAC with other techniques

We have seen that size and shape are sensitive for nodal metastases and that internal architecture and USFNAC are specific. Only three studies have attempted to directly compare US and USFNAC with other imaging techniques in staging N0 HNSCC but cross referencing between them is difficult because of variations in tumour type, nodal stage, imaging protocols, histopathological techniques and criteria for malignancy.

In 1998, Takes *et al.* published a study from five centres comparing US+USFNAC with CT in 50 patients with N0 HNSCC, eight of whom had received previous radiotherapy to the neck[51]. The CT criteria for metastases were nodes >1 cm, round shape, rim enhancement and central necrosis. The criteria for USFNAC varied between sites from an unspecified diameter of >5 mm in a high risk area to two of five morphological features combined with unspecified diameter of >7 mm. CT was more sensitive (54% vs 48%) whilst US+USFNAC was more specific (100% vs 92%) but the accuracy was the same at 78%. Furthermore there was no apparent advantage to combining the two techniques. They concluded that a watch and wait policy could not be justified as both US+USFNAC and CT missed around 50% of occult metastases. The sensitivity of both CT and USFNAC was very low in this study which has been difficult to explain.

Atula *et al.* compared CT, US and USFNAC in 86 patients with a mixture of N0 head and neck tumours[57]. The criteria for malignancy on CT and US were a minimum axial diameter of >10 mm, three or more nodes with minimum diameter >8 mm found grouped together or the presence of necrosis. USFNAC was performed on all readily visible nodes bilaterally. Thirty-one percent of N0 necks were upstaged by imaging of which only half were positive on US alone. All metastatic nodes detected by CT and missed on US were positive on USFNAC but USFNAC detected additional metastases in a further five patients. The authors concluded that USFNAC should be performed in HNSCC irrespective of the use of CT or MRI.

The third paper came from Van den Brekel *et al.* and is the only series to directly compare CT, MRI, US and USFNAC in N0 HNSCC[58]. The study population was 132 patients who underwent a total of 180 neck dissections including 88 that were clinically N0. In the N0 subgroup, the US criteria for malignancy were based on size with a cut-off of 8 mm (9 mm for level Ib) and grouping of three or more borderline lymph nodes. The criteria for CT and MRI included a size cut-off of 7 mm, the presence of necrosis and grouping as above. USFNAC was performed on any node with minimum short axis diameter >4 mm. In this group of patients USFNAC performed significantly better than any other technique with a sensitivity of 73%, specificity of 100% and accuracy of 86% compared to 68% for US alone, 66% for CT and 75% for MRI.

So in experienced hands US with USFNAC is probably the most accurate technique for staging lymph nodes in N0 HNSCC and may be good enough to bring the probability of OM to <0.2 thereby permitting a watch and wait policy. van den Brekel's team adopted this policy and subsequently published a series of 77 patients with clinically N0 HNSCC managed this way[59]. USFNAC was performed on any node >4 mm in minimum short axis diameter and those patients staged N0 were managed conservatively with regular clinical and US review. The nodal recurrence rate was 18% of which two-thirds were treated successfully. As the NPV of this staging strategy was >0.8 van den Brekel's team felt able to justify a watch and wait policy.

Positron emission tomography (PET), ultra-small superparamagnetic iron oxide particles (USPIOs) and sentinel lymph node biopsy (SNLB) are still under evaluation for staging lymph node metastases. Most series directly comparing PET with cross-sectional imaging involve small patient numbers, mixed pathology or ill-defined staging criteria[60–75]. Of these, only a few assess the role of PET in N0 HNSCC[10,70,71], reporting a sensitivity for occult metastasis varying from 0 to 78%. The minimum spatial resolution of PET is poor (4–5 mm) which likely explains the high false negative rates reported in sub-centimetre nodes[10,71]. Similarly, false positive rates due to the presence of inflammation and granulation tissue are high[72,73]. Although the use of PET is limited by availability and cost, it has the advantage of detecting synchronous tumours and distant metastases which are found in 9–21% of cases[67,74,75]. For this reason alone PET should be considered in the work-up of HNSCC.

USPIOs act as a functional negative MRI contrast agent. When administered intravenously, the particles are taken up by normal and reactive but not metastatic lymph nodes. Initial results from Mack *et al.* are promising in HNSCC, with a sensitivity of 86% and specificity of 100% on a node-by-node basis and an accuracy of 96% in level-by-level analysis[76,77]. However, when restricted to the N0 subgroup, USPIOs performed no better than MRI alone. The sensitivity for metastases was ≥20% with a specificity of ≥84%. The sub-optimal sensitivity in the N0 sub-group was due to in part to a failure to detect subtle partial infiltration; 98% of the metastatic nodes were less than 1 cm in size and about 25% were <3 mm.

SLNB was first developed to detect micrometastases in malignant melanoma[78]. The objective is to identify and selectively biopsy the sentinel node in order to determine whether completion lymphadenectomy is required. This relies on the assumption that metastases spread without skipping sentinel nodes and that there is no

cross contamination between nodal basins, but there is concern that this may not be the case in HNSCC. A discrepancy of 40–60% between lymphatic drainage patterns determined by lymphoscintigraphy and previously accepted anatomical charts has been described[79,80]. Civantos *et al.* reported two cases of clinically N0 HNSCC in which tumour infiltration had apparently resulted in redirection of lymphatic flow because the sentinel node was distal to other clearly diseased nodes[81]. Furthermore it now seems likely that there is often more than one sentinel node in HNSCC[82].

Nevertheless SLNB has had promising results in HNSCC. Vital dyes, radioisotopes and microbubble contrast agents have been used in varying combinations with open dissection, USFNAC and PET[9,71,81–85]. Ross *et al.* pooled data of SNLB in 61 clinically N0 HNSCC patients from 22 centres[9]. Forty-four percent were positive for metastases of which 18.5% had micrometastases only. A sentinel node was detected in 93% of the positive cases and was the only involved node in 63%. Werner *et al.* performed SNLB in 90 patients with N0 HNSCC staged on the basis of US using >1 cm in two dimensions, spherical shape or diffuse borders of the capsule as the criteria for malignancy[82]. Up to three sentinel nodes were biopsied in each patient. SNLB correctly staged patients in 97% with a sensitivity of 96.7%. However, if SNLB had been limited to only one node, 39% of positive necks would have been missed.

Nieuwenhuis *et al.* took a cohort of 161 patients with N0 HNSCC staged by USFNAC using minimal axial diameter size criteria of 3 mm at level 1 and 4 mm at all other levels[85]. Between zero and four aspirates were performed per neck side. In 39 cases, USFNAC was guided by sentinel node lymphoscintigraphy using a hand-held gamma camera to locate the node. All metastasis negative patients were managed by a watch and wait policy. Twenty-one percent developed lymph node metastases and were treated with surgery and post-operative radiotherapy of which 79% were salvaged, i.e. using this management protocol only 7/161 patient died of recurrent disease. They concluded that, although it was possible to identify the sentinel node with US, it did not influence the rate of recurrence.

Conclusion

Micrometastases are the isolated manifestation of metastatic disease in around 8% of patients with clinically N0 HNSCC and are beyond detection by any currently available imaging technique. The consequence of leaving micrometastases untreated is unknown and until this is resolved, debate over the need for treatment of the neck will continue. The primary goal of nodal staging should be to detect occult metastases amongst nodes that would otherwise not be destined for elective treatment. In skilled hands, US with USFNAC is the most accurate method currently available although cross-sectional imaging is still required to assess nodes at inaccessible locations. An L/T ratio ≤ 2, non-hilar vascular pattern, parenchymal granular echoes, necrosis and the presence of groups of three or more otherwise normal nodes in a high risk area are good indicators of macrometastatic disease (Table 5) but the best published results used exacting size criteria to select nodes for USFNAC. Research into SLNB and USPIOs is promising but at present validation of these techniques is still incomplete.

Table 5 US features suggestive of lymph node metastases

L/T ratio ≤ 2
Non-hilar vascular pattern
Parenchymal granular echoes
Necrosis
Extracapsular spread
Three or more normal looking nodes grouped in a high risk area

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